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PATENT

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10/16/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Emily M. Stuart

Applicant	:	Ken Kasper, et al.
Application No.	:	09/368,010
Filed	:	August 3[illegible], 1999
Title	:	MONOCLONAL ANTIBODIES TO TACROLIMUS AND IMMUNOASSAY METHODS FOR TACROLIMUS
Grp./Div.	:	1641
Examiner	:	M.E. Ceperley
Docket No.	:	45011/MBF/D542

SUBMISSION OF APPELLANT'S REPLY BRIEF TO EXAMINER'S ANSWER
37 C.F.R. § 1.193(b) (1)

Assistant Commissioner for Patents
Washington, D.C. 20231

Post Office Box 7068
Pasadena, CA 91101-7068
September 30, 2002

Commissioner:

Enclosed for filing are the **original and two copies** of Appellant's Reply Brief to the Examiner's Answer for this application.

The Commissioner is hereby authorized to charge any further fees under 37 CFR 1.16 and 1.17 which may be required by this paper to Deposit Account No. 03-1728. Please show our docket number with any charge or credit to our Deposit Account. **A copy of this letter is enclosed.**

Respectfully submitted,

CHRISTIE, PARKER & HALE, LLP

By _____
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45011/MBF/D542

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	K. Kasper et al.	Examiner:	M.E. Ceperley
Serial No:	09/368,010	Group Art Unit:	1641
Filed:	August 23, 1999	Docket:	45011/MBF/D542
Due Date:	September 30, 2002	Date Mailed:	September 30, 2002

Title: MONOCLONAL ANTIBODIES TO TACROLIMUS AND IMMUNOASSAY METHODS FOR TACROLIMUS

REPLY BRIEF TO EXAMINER'S ANSWER UNDER 37 C.F.R. § 1.193(b)(1)

Box AF
Honorable Commissioner for Patents
Washington, D.C. 20231

Gentlemen:

Appellant replies to the Examiner's Answer (Paper No. 18) as follows:

The Examiner continues to reject claims 11-12, 31-33, 50-51, and 61 under the first paragraph of 35 U.S.C. § 112 as based on a specification that fails to provide an adequate enabling disclosure to enable one skilled in the art to reproducibly make the claimed antibodies without undue experimentation.

Appellant considers that the specification, including the working example, does provide sufficient guidance to one of ordinary skill in the art to enable such a person to reproducibly make the claimed antibodies in light of the generally-accepted reproducibility of the technology. The degree of guidance given in the specification, including the working example, is in accord with the case law generally governing the application of the first paragraph of 35 U.S.C. § 112. Specifically, the degree of guidance, including the working example, is in accord with case law deciding the issue in

this technological area. The Patent and Trademark Office is bound by this case law in the absence of factors that enable it to be distinguished. Such factors are completely absent here.

The Examiner's Answer lays great stress on the fact that the monoclonal antibody of claim 11 has specific characteristics in terms of binding affinity and cross-reactivity. Specifically, this monoclonal antibody is stated to have a binding affinity of about 3.7×10^9 liters/mole, cross-reactivity with 13-demethyl tacrolimus, and less than about 8% cross-reactivity with all of the following tacrolimus metabolites: 15-demethyl tacrolimus, 31-demethyl tacrolimus, 13,31-didemethyl tacrolimus, 15,31-didemethyl tacrolimus, and 12-hydroxy tacrolimus.

The Examiner's answer states, without providing any evidence or reasoning, that there is insufficient information in the specification to enable one of ordinary skill in the art to prepare even a single example of a monoclonal antibody meeting these limitations. The fact that there is an example of such a monoclonal antibody in Example 2, which is described in detail at page 30, line 27 to page 31, line 3 of the specification.

In maintaining the rejection under the first paragraph of 35 U.S.C. § 112, the Examiner places great importance on these specific characteristics of the monoclonal antibody. The Examiner posits an inexact analogy of "screening for a person who has all of the following characteristics: a) a certain index of refraction of the iris of the eye; b) a specific subset of fingerprint characteristics; c) a certain hair color; d) a certain age within days; e) certain ethnicity; and f) certain specific genes" (Examiner's Answer, p.4, lines 17-20).

This analogy is inaccurate. There is no practical, much less moral, method of growing large numbers of human beings in culture, but very large numbers of hybridomas can be isolated and grown in culture in a relatively brief period of time. Moreover, there is no way to screen large numbers of human beings for any of these

characteristics in a brief period of time. Screening for any of these characteristics takes a relatively long time and must be done individually for each person to be screened. For example, measurement of the index of refraction must be done using complex equipment and requires dilation of the pupils of the eye. Determination of ethnic origin, to the extent that it can be done at all, requires interviewing each individual. There is no way that 96 individuals at a time can be placed in wells of an assay plate and assayed for such characteristics, but this type of mass screening can be done routinely for hybridomas. These assays use techniques that have been highly developed, such as enzymatic immunoassay, radioimmunoassay, and other assay techniques. The result of the development of the technology is that hundreds of hybridomas can be screened in a short time for activity, affinity, and cross-reactivity. Thus, the analogy breaks down with respect to the work required to screen and the time required to screen. Enablement must be judged with respect to the technology employed by one of ordinary skill in the art.

There is no reason to doubt, from the specification, that one of ordinary skill in the art could reproduce the claimed invention without undue experimentation. Moreover, there has been no reasoning provided to substantiate or support the assertion that "it would be unreasonable to assume that one skilled in the art could obtain even a single monoclonal antibody meeting the specifications of claim 11 if he prepared and used the immunogenic conjugate described in the working example and screened a very large number of hybridomas" (Examiner's Answer, p. 4, lines 3-6). There is no evidence that any of the cloning or screening steps required would entail an unreasonable amount of effort or require an extended time. Without reasoning that would actually lead to a conclusion of undue experimentation, there can be no proper basis for a rejection under the first paragraph of 35 U.S.C. § 112 on the grounds of lack of enablement. In re Marzocchi, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971); In re Wright, 999 F.2d 1557, 27 U.S.P.Q. 2d 1510 (Fed. Cir. 1993).

The fact that a considerable amount of experimentation may be required does not lead to a conclusion of undue experimentation as long as there is sufficient guidance in the specification and the experimentation required is routine in nature. In re

Colianni, 561 F.2d 220, 195 U.S.P.Q. 150 (C.C.P.A. 1977); In re Jackson, 217 U.S.P.Q. 804 (Bd. Pat. App. 1982).

The fact that Appellant is in possession of what the Examiner presumes is the sole working example of the claimed invention yet made is not a proper basis for rejection of the claims under the first paragraph of 35 U.S.C. § 112. The proper test is whether the specification provides sufficient teaching so that one skilled in the art can "make and use the claimed invention without 'undue experimentation.'" In re Wright, 999 F.2d at 1561, 27 U.S.P.Q. 2d at 1513. Indeed, not a single working example is *necessarily* required by the statutory provision. In re Long, 369 F.2d 892, 895, 151 U.S.P.Q. 640, 642 (C.C.P.A. 1966). For example, if someone filed a patent application on a high-performance cylinder head for a car, it would not matter if he had the only actual working example, as long as the materials, dimensions, and machining operations required for the building of the cylinder head were disclosed with sufficient specificity in the specification. Application of the proper test leads to the result that Appellant is entitled to a patent on this hybridoma.

The proper test in the art of monoclonal antibody preparation is not the number of unsuccessful hybridomas tested. Rather, it is the degree of experimentation required to yield a successful hybridoma. In re Wands, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988). Indeed, the court in Wands expressly stated that the fact that there was a relatively high fraction of failures in the monoclonal antibody production process was not a proper basis for a rejection under the first paragraph of 35 U.S.C. § 112. Id.

As emphasized by the court in Johns Hopkins University v. CellPro, Inc., 152 F.3d 1342, 47 U.S.P.Q. 1705 (Fed. Cir. 1998), a certain amount of experimentation, and even a certain amount of failure, is expected in the optimization of the Kohler-Milstein process for the production of monoclonal antibodies. This degree of experimentation and the failure of some trials does not constitute undue experimentation or lead to a conclusion of lack of enablement under the first paragraph of 35 U.S.C. § 112. Id.

Although a deposit *may* be a way of satisfying the requirements for enablement under the first paragraph of 35 U.S.C. § 112, there is no requirement for a deposit if the requirements are met by the disclosure as it would be understood by one skilled in the art. Tabuchi v, Nubel, 559 F.2d 1183, 194 U.S.P.Q. 2d 521 (C.C.P.A. 1977); Ex parte Hata, 6 U.S.P.Q. 2d 1652 (Bd. Pat. App. & Int'f 1987). Similarly, no deposit was actually required in Wands itself. The court in Wands held that the starting materials for producing high-affinity IgM antibodies against hepatitis B surface antigen were readily available and the required techniques were either well-known to the public or had been described in the specification. Wands, 858 F.2d at 731, 8 U.S.P.Q. 2d at 1400. It should be noted that the IgM monoclonal antibodies claimed in Wands are relatively unusual; most monoclonal antibodies are IgG.

The Patent Rules, at 37 C.F.R. § 1.802(b), correctly state the situation when a deposit is required:

> Biological material need not be deposited unless access to such material is necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112. If a deposit is necessary, it shall be acceptable if made in accordance with these regulations. Biological material need not be deposited, *inter alia*, if it is known and readily available to the public or can be made or isolated without undue experimentation.

Similarly, the Manual of Patent Examining Procedure, at M.P.E.P. § 2404.02, states that a deposit is not required when the biological materials can be obtained without undue experimentation:

> Applicant may show that a deposit is not necessary even though specific biological materials are required to practice the invention if those biological materials can be made or isolated without undue

experimentation. Deposits may be required to support the claims if an isolation procedure requires undue experimentation to obtain the desired biological material. *Ex Parte Jackson*, 217 USPQ 804 (Bd. App. 1982). No deposit is required, however, where the required biological materials can be obtained from publicly available material with only routine experimentation and a reliable screening test. *Tabuchi v. Nubel*, 559 F.2d 1183, 194 USPQ 521 (CCPA 1977); *Ex Parte Hata*, 6 USPQ2d 1652 (Bd. Pat. App. & Int. 1987).

Thus, the situation here is covered by the Patent Rules and Manual of Patent Examining Procedure, and no deposit is required.

Accordingly, the Board of Patent Appeals and Interferences is respectfully requested to reverse this rejection and remand this application to the Primary Examiner with directions to pass this application to issue.

Respectfully submitted:

Date: September 30, 2002

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